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Comparison of Everolimus- and Paclitaxel-Eluting Stents in Patients With Acute and Stable Coronary Syndromes

Pooled Results From the SPIRIT (A Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) and COMPARE (A Trial of Everolimus-Eluting Stents and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice) Trials

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Objectives This study sought to compare the clinical outcomes of everolimus-eluting stents (EES) versus paclitaxel-eluting stents (PES) in patients with acute coronary syndromes (ACS) and stable coronary artery disease (CAD).

Background Although randomized trials have shown superiority of EES to PES, the safety and efficacy of EES in ACS is unknown.

Methods We performed a patient-level pooled analysis from the prospective, randomized SPIRIT (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) II, III, IV, and COMPARE (A Trial of Everolimus-Eluting Stents and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice) trials in which 2,381 patients with ACS and 4,404 patients with stable CAD were randomized to EES or to PES. Kaplan-Meier estimates of death, myocardial infarction (MI), ischemia-driven target lesion revascularization, and stent thrombosis were assessed at 2 years and stratified by clinical presentation (ACS vs. stable CAD).

Results At 2 years, patients with ACS compared with stable CAD had higher rates of death (3.2% vs. 2.4%, hazard ratio [HR]: 1.37 [95% confidence interval (CI): 1.02 to 1.85], $p = 0.04$) and MI (4.9% vs. 3.4%, HR: 1.45 [95% CI: 1.14 to 1.85], $p = 0.02$). In patients with ACS, EES versus PES reduced the rate of death or MI (6.6% vs. 9.3%, HR: 0.70 [95% CI: 0.52 to 0.94], $p = 0.02$), stent thrombosis (0.7% vs. 2.9%, HR: 0.25 [95% CI: 0.12 to 0.52], $p = 0.0002$), and ischemia-driven target lesion revascularization (4.7% vs. 6.2%, HR: 0.69 [95% CI: 0.48 to 0.99], $p = 0.04$). In patients with stable CAD, EES reduced the rate of death or MI (4.5% vs. 7.1%, HR: 0.62 [95% CI: 0.48 to 0.80], $p = 0.0002$), stent thrombosis (0.7% vs. 1.8%, HR: 0.34 [95% CI: 0.19 to 0.62], $p = 0.0002$), and ischemia-driven target lesion revascularization (3.9% vs. 6.9%, HR: 0.55 [95% CI: 0.42 to 0.73], $p < 0.0001$).

Conclusions Treatment with EES versus PES provides enhanced safety and efficacy regardless of the acuity of the clinical syndrome being treated and appears to mitigate the increased risk of stent thrombosis associated with ACS. (A Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients With de Novo Native Coronary Artery Lesions [SPIRIT II]; NCT00180310; SPIRIT III: A Clinical Evaluation of the Investigational Device XIENCE V Everolimus Eluting Coronary Stent System [EECSS] in the Treatment of Subjects With de Novo Native Coronary Artery Lesions [SPIRIT III]; NCT00180479; SPIRIT IV Clinical Trial: Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Subjects With de Novo Native Coronary Artery Lesions [SPIRIT IV]; NCT00307047; A Trial of Everolimus-Eluting Stents and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice: the COMPARE Trial [COMPARE]; NCT01016041) (J Am Coll Cardiol Intv 2011;4:1104–15) © 2011 by the American College of Cardiology Foundation

Drug-eluting stents (DES) substantially reduce angiographic restenosis and the clinical need for repeat revascularization procedures (1,2). Nevertheless, despite some evidence of their safety in patients with acute coronary syndromes (ACS) (3–5), the routine use of DES in ACS remains controversial (6–8). Furthermore, there are no randomized studies comparing different types of DES in ACS patients.

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Second-generation DES were designed in part to address lingering concerns regarding DES safety and late stent thrombosis, especially in high-risk patients. In the everolimus-eluting stent(s) (EES), the antiproliferative agent everolimus, a rapamycin analog, is released from a thin, biocompatible fluorocopolymer that is deployed on a low-profile (81-μm strut thickness), flexible cobalt chromium stent (9). In the paclitaxel-eluting stent(s) (PES), paclitaxel is released from a styrene-isoprene-butadiene-styrene copolymer, deployed on a stainless steel stent with 132- or 97-μm strut thickness (Taxus Express2 and Taxus Liberté, respectively, Boston Scientific, Natick, Massachusetts) (10,11).

Several randomized trials and real-world registries have shown superior safety and efficacy of EES versus a commonly used PES (9,12–16). However, these studies were underpowered for subgroup analysis of high-risk patients with ACS, especially for the detection of differences in uncommon events, such as stent thrombosis. Consequently, the relative safety and efficacy of EES in patients with ACS has not been established. Therefore, we sought to compare the clinical outcomes of EES versus PES in patients with ACS and stable coronary artery disease (CAD). To achieve sufficient power to address this question, we performed a patient-level pooled analysis from the 4 completed randomized trials comparing EES with PES.

Methods

Patient population and study procedure. We combined the databases from the SPIRIT II (A Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients With de Novo Native Coronary Artery Lesions), SPIRIT III (A Clinical Evaluation of the Investigational Device XIENCE V Everolimus Eluting Coronary Stent System (EECSS) in the Treatment of Subjects With de Novo Native Coronary Artery Lesions), SPIRIT IV (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Subjects With de Novo Native Coronary Artery Lesions), and COMPARE (A Trial of Everolimus-Eluting Stents and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice) trials. The protocol and principal results of each trial have been published elsewhere (12,13,15,17). The major characteristics of each trial are presented in Table 1. Briefly, each study was a prospective, single-blind, controlled clinical trial in which patients were randomized to receive either EES (manufactured as Xience V by Abbott Vascular, Santa Clara, California, and also distributed as PROMUS by Boston Scientific) or PES (Taxus Express2, or Taxus Liberté, Boston Scientific). SPIRIT II enrolled 300 patients with up to 2 de novo native coronary lesions. SPIRIT III enrolled 1,002 patients, with inclusion criteria similar to the SPIRT II trial. SPIRIT IV enrolled 3,687 patients with up to 3 de novo native coronary artery lesions. Even though patients with unstable angina were enrolled, the SPIRIT trials excluded many high-risk patients, including those with acute or recent myocardial infarction (MI) or visible thrombus. The COMPARE trial enrolled 1,800 unselected patients with no exclusion criteria based on symptoms or lesion types. Patients with ST-segment elevation myocardial infarction (STEMI) and non-STEMI were actively recruited in COMPARE. Clinical endpoints in all trials were adjudicated by a clinical events committee blinded to stent assignment.

Abbreviations and Acronyms

ACS = acute coronary syndrome(s)
CAD = coronary artery disease
CI = confidence interval
DES = drug-eluting stent(s)
EES = everolimus-eluting stent(s)
HR = hazard ratio
ID-TLR = ischemia-driven target lesion revascularization
MI = myocardial infarction
PES = paclitaxel-eluting stent(s)
STEMI = ST-segment elevation myocardial infarction

For the current pooled analysis, the clinical endpoints of all-cause and cardiac death, MI, ischemia-driven target lesion revascularization (ID-TLR), and their composites at

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Table 1. Characteristics of the Included Studies

	SPIRIT II	SPIRIT III	SPIRIT IV	COMPARE
Number randomized	300	1,002	3,687	1,800
Geography	Multicenter, non-U.S.	Multicenter, U.S.	Multicenter, U.S.	Single-center, the Netherlands
Stent platform				
EES	Xience V	Xience V	Xience V	Xience V
PES	Taxus Express2	Taxus Express2	Taxus Express2	Taxus Liberté
Patients with ACS, %	28.3	20.5	27.6	59.8
Patients with diabetes, %	23.1	29.0	32.2	18.1
Reference vessel diameter, mm, mean ± SD	2.73 ± 0.54	2.76 ± 0.46	2.68 ± 0.50	2.63 ± 0.60
Lesion length, mm, mean ± SD	13.04 ± 5.90	14.71 ± 5.62	14.70 ± 6.65	22.42 ± 17.41
Planned angiographic follow-up, months	6 and 24	8	None	None

ACS = acute coronary syndrome(s); EES = everolimus-eluting stent(s); PES = paclitaxel-eluting stent(s).

2 years were compared by the randomized treatment arms and stratified by clinical presentation: ACS (including unstable angina, non–STEMI, and STEMI), and stable CAD. Stent thrombosis was determined using the Academic Research Consortium definite or probable definition (18) and was subclassified as early (<30 days), late (30 days to 1 year), and very late (1 to 2 years).

Statistical analysis. All analyses were performed according to intention-to-treat. Binary variables are summarized as counts and percentages and were compared using chi-square or the Fisher exact test, as appropriate. Continuous variables are summarized as mean ± SD and were compared using *t* tests. Two-year outcomes are displayed as time-to-event event curves, summarized as Kaplan-Meier estimates, and compared using log-rank tests and hazard ratios. Landmark analysis was used to determine the rates of early, late, and very late stent thrombosis. Cox proportional hazards models with forward stepwise selection were used to adjust for differences in baseline characteristics. A combined odds ratio (95% confidence interval [CI]) for the 2-year composite rates of cardiac death, MI, or ID-TLR was calculated in the ACS and stable CAD cohorts using a fixed-effects meta-analysis (inverse-variance weighted). Heterogeneity was tested with Cochran *Q* via a chi-square test. All statistical tests were 2-tailed. A p value of 0.05 was used for statistical significance.

Results

The pooled patient-level analysis of the SPIRIT II, SPIRIT III, SPIRIT IV, and COMPARE trials included 6,789 patients, among whom ACS status was known in 6,785. A total of 2,381 (35%) patients presented with ACS, of whom 1,393 (59%) were randomized to EES and 988 (41%) to PES. Among 4,404 (65%) patients that presented with stable CAD, 2,854 (65%) received EES and 1,550 (35%) received PES. Tests of interactions between source trial and stent type on 2-year clinical outcomes were all nonsignificant (p = 0.58, 0.83, and 0.32 for death; composite cardiac death, MI, or ID-TLR; and definite or probable stent thrombosis, respectively), justifying pooling of the 4 studies.

Outcomes in patients with ACS versus stable CAD. Compared with patients with stable CAD, patients with ACS were younger (62.4 ± 11.2 years vs. 63.6 ± 10.3 years) and had lower rates of diabetes (24.6% vs. 29.1%), hypertension (59.7% vs. 73.4%), and hyperlipidemia (60.3% vs. 73.3%), but a higher rate of smoking (32.9% vs. 20.7%) (p < 0.0001 for all). Patients with ACS also had higher rate of TIMI (Thrombolysis In Myocardial Infarction) flow grade 0/1 at baseline (14.8% vs. 4.2%), and coronary thrombus (18.9% vs. 2.5%), and they were treated with longer stents (35.9 ± 25.6 mm vs. 31.2 ± 21.7 mm) (p < 0.0001 for all). At 2 years, patients with ACS compared with those with stable CAD had higher rates of death (3.2% vs. 2.4%, hazard ratio [HR]: 1.37 [95% CI: 1.02 to 1.85], p = 0.04), MI (4.9% vs. 3.4%, HR: 1.45 [95% CI: 1.14 to 1.85], p = 0.02), and Academic Research Consortium definite or probable stent thrombosis (1.6% vs. 1.1%, HR: 1.54 [95% CI: 1.00 to 2.38], p = 0.05), with similar rates of ID-TLR (5.4% vs. 4.9%, HR: 1.06 [95% CI: 0.85 to 1.33], p = 0.56).

Baseline characteristics according to stent type. As shown in Table 2, among patients with ACS, those randomized to EES versus PES were less frequently men and were more likely to have hyperlipidemia and prior MI. Patients randomized to EES were also less likely to have moderate or severe calcification or thrombus, and they had slightly shorter lesions but in smaller vessels. In the stable CAD cohort, patients treated with EES versus PES had a higher rate of hypertension and lower rates of total occlusions and calcified vessels, with a slightly larger reference vessel diameter. The rates of aspirin and thienopyridine use with both stents at discharge and at the 1-year landmark were not significantly different in patients with ACS and stable CAD.

Clinical outcomes according to randomized stent type. Treatment with EES versus PES resulted in significantly lower rates of adverse clinical outcomes in both the ACS

Table 2. Baseline Characteristics and Antiplatelet Agent Use

Variable	ACS			Stable CAD		
	EES (n = 1,393)	PES (n = 988)	p Value	EES (n = 2,854)	PES (n = 1,550)	p Value
Demographics						
Age, yrs	62.1 ± 11.2	62.7 ± 10.9	0.19	63.5 ± 10.2	63.7 ± 10.4	0.50
Male	65.5% (912)	71.6% (707)	0.002	70.0% (1,999)	68.3% (1,058)	0.23
Diabetes mellitus	26.0% (362)	22.7% (224)	0.07	29.0% (826)	29.5% (456)	0.75
Insulin-treated	6.5% (91)	6.7% (66)	0.87	7.7% (219)	7.6% (118)	1.00
Current smoking	33.3% (457)	32.4% (316)	0.66	20.9% (585)	20.3% (308)	0.69
Hypertension	61.2% (852)	57.7% (569)	0.10	74.5% (2,124)	71.4% (1,106)	0.03
Hyperlipidemia	63.1% (869)	56.4% (553)	0.001	74.1% (2,080)	71.9% (1,104)	0.11
Prior CABG	6.7% (93)	5.6% (55)	0.30	7.5% (213)	6.3% (98)	0.18
Prior MI	22.9% (312)	18.6% (181)	0.01	19.1% (535)	19.2% (294)	0.97
Prior PCI	13.3% (184)	12.3% (121)	0.49	15.1% (426)	14.9% (228)	0.86
Presenting diagnosis						
Stable angina	0.0% (0)	0.0% (0)	—	80.5% (2,254)	82.2 (1,248)	0.18
Unstable angina	68.8% (959)	56.6% (559)	<0.0001	0.0% (0)	0.0% (0)	—
Non–STEMI	13.9% (194)	22.0% (217)	<0.0001	0.0% (0)	0.0% (0)	—
STEMI	17.2% (240)	21.5% (212)	0.01	0.0% (0)	0.0% (0)	—
Target lesion characteristics						
RCA	34.8% (644)	35.4% (467)	0.73	33.8% (1,221)	32.7% (664)	0.41
LAD	39.0% (720)	37.4% (493)	0.39	41.2% (1,489)	41.1% (834)	0.93
LCX	25.7% (475)	26.3% (347)	0.71	24.6% (889)	25.7% (521)	0.39
Left main	0.5% (9)	0.8% (11)	0.26	0.4% (13)	0.5% (11)	0.39
SVG	1.0% (19)	1.1% (14)	1.00	0.2% (8)	0.5% (10)	0.09
Total occlusion	4.1% (76)	5.5% (72)	0.09	0.9% (33)	2.2% (45)	0.0001
Moderate or severe calcification	16.2% (298)	19.7% (259)	0.01	13.3% (477)	16.7% (337)	0.0006
Thrombus	16.3% (300)	22.6% (297)	<0.0001	2.6% (92)	2.4% (49)	0.79
Lesion length, mm	17.0 ± 11.1	18.4 ± 14.2	0.01	15.5 ± 8.6	15.9 ± 9.7	0.14
RVD, mm	2.66 ± 0.52	2.72 ± 0.56	0.005	2.69 ± 0.51	2.66 ± 0.52	0.04
MLD, mm	0.76 ± 0.44	0.81 ± 0.48	0.003	0.82 ± 0.41	0.83 ± 0.42	0.25
Diameter stenosis, %	71.9 ± 15.8	70.9 ± 16.7	0.11	69.5 ± 14.0	68.7 ± 14.6	0.06
Antiplatelet therapy						
Discharge						
Aspirin	96.3% (1,333)	96.9% (950)	0.42	97.8% (2,790)	96.8% (1,501)	0.07
Thienopyridine	99.1% (1,372)	99.6% (976)	0.21	99.4% (2,836)	99.2% (1,538)	0.57
1 yr						
Aspirin	93.7% (1,283)	92.7% (892)	0.36	93.7% (2,646)	92.6% (1,423)	0.20
Thienopyridine	82.0% (1,122)	80.0% (770)	0.26	81.6% (2,306)	82.0% (1,260)	0.77

Values are mean ± SD or % (n).

CABG = coronary artery bypass graft; CAD = coronary artery disease; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; MI = myocardial infarction; MLD = minimal luminal diameter; PCI = percutaneous coronary intervention; RCA = right coronary artery; RVD = reference vessel diameter; STEMI = ST-segment elevation myocardial infarction; SVG = saphenous vein graft; other abbreviations as in Table 1.

and stable CAD groups. In the ACS cohort (Table 3, Fig. 1), patients treated with EES rather than PES had a lower rate of ID-TLR at 30 days, and lower rates of MI (especially Q-wave MI), death or MI, and ID-TLR at 2 years. Similarly, in the stable CAD cohort (Table 4, Fig. 2), treatment with EES rather than PES resulted in significantly lower rates of MI, death or MI, and ischemic TLR at 30 days and 2 years. The odds ratio for the composite of cardiac death, MI, or ID-TLR at 2 years for EES versus PES by the individual source trial and combined meta-analysis is shown in Figure 3. Significant heterogeneity was not present among the individual trial outcomes.

Multivariable analysis was performed to adjust for differences in baseline patient and lesion characteristics. Adjusted hazard ratios were very similar to unadjusted hazard ratios in

Table 3. Clinical Outcomes in Patients Presenting With an ACS According to Randomized Stent

	EES	PES	HR (95% CI)	p Value
30-day outcomes				
Death, all-cause	0.6% (8)	0.5% (5)	1.14 (0.37–3.47)	0.82
Cardiac death	0.5% (7)	0.5% (5)	0.99 (0.32–3.13)	0.99
Noncardiac death	0.1% (1)	0.0% (0)	N/A	0.40
MI, all	1.7% (23)	2.4% (24)	0.68 (0.38–1.20)	0.18
Q-wave MI	0.3% (4)	0.6% (6)	0.47 (0.13–1.67)	0.23
Non–Q-wave MI	1.4% (19)	1.8% (18)	0.75 (0.39–1.43)	0.38
ID-TLR	0.3% (4)	1.2% (12)	0.24 (0.08–0.73)	0.006
Death or MI	2.2% (30)	2.8% (28)	0.76 (0.45–1.27)	0.29
Cardiac death or MI	2.1% (29)	2.8% (28)	0.73 (0.44–1.23)	0.24
Death, MI, or ID-TLR	2.4% (33)	2.9% (29)	0.81 (0.49–1.33)	0.40
Cardiac death, MI, or ID-TLR	2.3% (32)	2.9% (29)	0.78 (0.47–1.29)	0.34
2-yr outcomes				
Death, all-cause	2.8% (39)	3.6% (35)	0.79 (0.50–1.25)	0.31
Cardiac death	1.4% (19)	1.9% (18)	0.75 (0.39–1.43)	0.38
Noncardiac death	1.5% (20)	1.8% (17)	0.84 (0.44–1.59)	0.58
MI, all	4.0% (54)	6.2% (60)	0.63 (0.44–0.91)	0.01
Q-wave MI	0.4% (5)	1.7% (15)	0.23 (0.08–0.64)	0.002
Non–Q-wave MI	3.6% (49)	4.8% (46)	0.75 (0.50–1.12)	0.16
ID-TLR	4.7% (60)	6.2% (60)	0.69 (0.48–0.99)	0.04
Death or MI	6.6% (91)	9.3% (91)	0.70 (0.52–0.94)	0.02
Cardiac death or MI	5.2% (71)	7.7% (75)	0.66 (0.48–0.92)	0.01
Death, MI, or ID-TLR	10.1% (136)	12.6% (123)	0.77 (0.60–0.98)	0.04
Cardiac death, MI, or ID-TLR	8.7% (116)	11.0% (107)	0.76 (0.58–0.98)	0.04
Stent thrombosis				
ARC definite	0.4% (6)	2.2% (21)	0.20 (0.08–0.50)	0.01
ARC probable	0.3% (4)	0.7% (7)	0.41 (0.12–1.39)	0.0008
ARC definite or probable	0.7% (10)	2.9% (28)	0.25 (0.12–0.52)	0.0002
Cardiac death, MI, or stent thrombosis	5.3% (72)	7.7% (75)	0.67 (0.49–0.93)	0.02

Events rates are summarized as Kaplan-Meier % (n of events).

ARC = Academic Research Consortium; CI = confidence interval; HR = hazard ratio; ID-TLR = ischemia-driven target lesion revascularization; NA = not applicable; other abbreviations as in Tables 1 and 2.

both cohorts (Table 5). No significant interactions in the relative treatment effects were found between the randomized stent type and ACS versus stable CAD presentation for the 2-year rates of death; death or MI; and death, MI, or ID-TLR (p = 0.73, 0.52, and 0.12, respectively).

Stent thrombosis. Randomization to EES versus PES resulted in a substantial reduction of stent thrombosis both in patients with ACS and stable CAD (Tables 2 and 3). The 2-year rates of stent thrombosis after EES were similar among patients with stable CAD and ACS (0.7% vs. 0.7%, respectively, p = 0.72). Conversely, the 2-year rates of stent thrombosis in patients treated with PES occurred in 1.8% and 2.9% of patients with stable CAD and ACS, respectively (p = 0.09). The 2-year rates of definite or probable stent thrombosis in patients with stable CAD, unstable angina, non-STEMI, and STEMI treated with EES were 0.7%, 0.4%, 1.6%, and 1.3%, respectively (p for trend = 0.19), compared with 1.8%, 1.5%, 6.1%, and 3.4%, respectively (p for trend = 0.0004) in patients treated with PES (Fig. 4). Treatment with EES rather than PES was associated with lower rates of stent thrombosis in the early, late, and very late periods (Fig. 5), in both the ACS and stable CAD cohorts.

Discussion

With more than 13,000 patient-years of follow-up, the present patient-level pooled analysis is the largest randomized comparison between any 2 DES to date. The main findings of the current analysis are: 1) the prognosis of patients with ACS in the entire cohort was worse than those with stable CAD, with higher 2-year rates of death, MI, and stent thrombosis; 2) treatment with EES versus PES markedly reduced the 2-year rates of adverse clinical events in both ACS and stable CAD patients; 3) treatment with EES also resulted in a substantial decrease in the rate of stent thrombosis, with reductions apparent throughout the

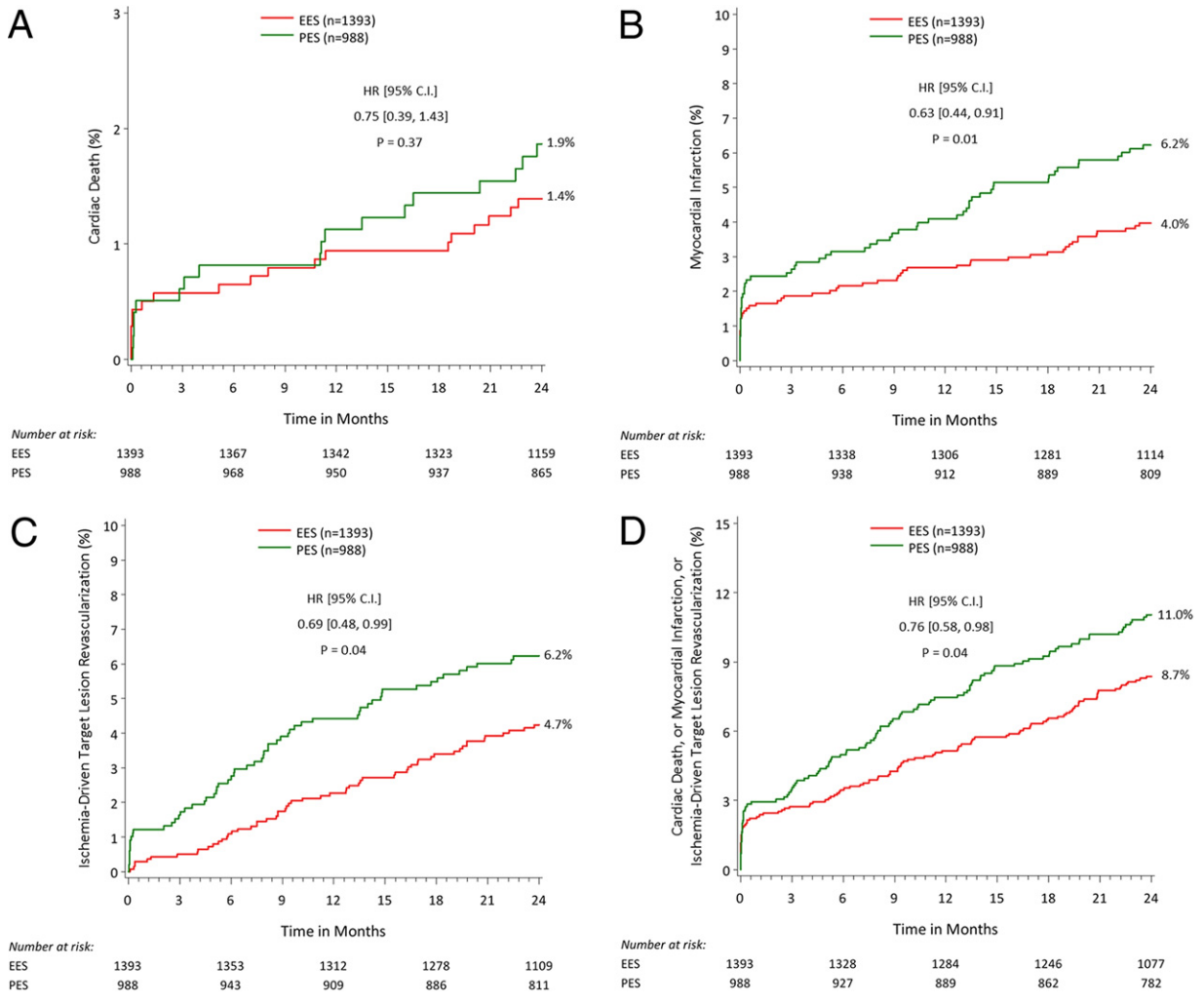

Figure 1. Time-to-Event Event Curves for Patients Presenting With ACS Randomized to EES Versus PES

Two-year cumulative event curves for cardiac death **(A),** myocardial infarction (MI) **(B),** ischemia-driven target lesion revascularization (ID-TLR) **(C),** and the composite of cardiac death, MI, or ID-TLR **(D).** ACS = acute coronary syndromes; CI = confidence interval; EES = everolimus-eluting stent(s); HR = hazard ratio; PES = paclitaxel-eluting stent(s).

2-year follow-up period in both patients with and without ACS.

Patients presenting with ACS most often have plaque rupture of a thin-cap fibroatheroma, which contains a large lipid core with thin fibrous cap, paucity of smooth muscle cells, and abundance of inflammatory cells (19). In contrast, atherosclerotic plaques in patients presenting with stable angina tend to have a thick fibrous cap rich in smooth muscle cells with a small or absent necrotic core (pathological intimal thickening). Different DES may have a differential impact on outcome in these 2 distinct clinical syndromes (20). Even though DES substantially reduce neointimal hyperplasia in stable plaques by inhibiting cell proliferation, migration, and extracellular matrix production, this mechanism may in theory be harmful in the setting of plaque rupture and a prothrombotic milieu, resulting in poor arterial healing and an increased risk for stent thrombosis (21). Indeed, the safety of the first-generation DES in ACS patients has been questioned (6–8). DES were not originally tested in patients with acute thrombotic syndromes in the trials leading to their regulatory approval, and thus are not indicated in ACS (22). Although accumulating data have demonstrated that the use of DES in ACS patients (including STEMI) is safe and reduces restenosis (3–5,23), no randomized clinical trials have compared different types of DES in these high-risk patients. Specifically, whether DES which are more potent at inhibiting neointimal growth than those which are less potent are favored in this setting is unknown.

Table 4. Clinical Outcomes in Patients Presenting With Stable CAD According to Randomized Stent

	EES	PES	HR (95% CI)	p Value
30-day outcomes				
Death, all-cause	0.0% (1)	0.1% (2)	0.27 (0.02–2.99)	0.25
Cardiac	0.0% (0)	0.1% (2)	—	0.06
Noncardiac	0.0% (1)	0.0% (0)	—	0.46
MI, all	1.4% (39)	2.6% (41)	0.51 (0.33–0.80)	0.002
Q-wave MI	0.1% (2)	0.3% (4)	0.27 (0.05–1.48)	0.11
Non–Q-wave MI	1.3% (37)	2.5% (38)	0.53 (0.34–0.83)	0.005
ID-TLR	0.4% (11)	1.0% (16)	0.37 (0.17–0.80)	0.009
Death or MI	1.4% (39)	2.7% (42)	0.50 (0.32–0.78)	0.002
Cardiac death or MI	1.4% (39)	2.7% (42)	0.50 (0.32–0.78)	0.002
Death, MI, or ID-TLR	1.4% (41)	3.2% (49)	0.45 (0.30–0.68)	0.0001
Cardiac death, MI, or ID-TLR	1.4% (41)	3.2% (49)	0.45 (0.30–0.68)	0.0001
2-yr outcomes				
Death, all-cause	2.3% (62)	2.6% (38)	0.88 (0.58–1.31)	0.52
Cardiac	1.1% (30)	1.3% (19)	0.85 (0.48–1.51)	0.57
Noncardiac	1.2% (32)	1.3% (19)	0.90 (0.51–1.59)	0.72
MI, all	2.4% (68)	5.1% (77)	0.47 (0.34–0.66)	<0.0001
Q-wave MI	0.1% (4)	0.9% (13)	0.17 (0.05–0.51)	0.0003
Non–Q-wave MI	2.3% (64)	4.4% (67)	0.51 (0.36–0.72)	<0.0001
ID-TLR	3.9% (107)	6.9% (102)	0.55 (0.42–0.73)	<0.0001
Death or MI	4.5% (124)	7.1% (107)	0.62 (0.48–0.80)	0.0002
Cardiac death or MI	3.4% (95)	5.8% (88)	0.58 (0.43–0.77)	0.0002
Death, MI, or ID-TLR	7.7% (213)	12.4% (185)	0.60 (0.49–0.73)	<0.0001
Cardiac death, MI, or ID-TLR	6.6% (184)	11.1% (166)	0.58 (0.47–0.72)	<0.0001
Stent thrombosis				
ARC definite	0.5% (14)	1.2% (18)	0.42 (0.21–0.84)	0.01
ARC probable	0.1% (4)	0.8% (12)	0.18 (0.06–0.56)	0.0008
ARC definite or probable	0.7% (18)	1.8% (28)	0.34 (0.19–0.62)	0.0002
Cardiac death, MI, or stent thrombosis	3.5% (98)	6.0% (90)	0.58 (0.44–0.77)	0.0002

Events rates are summarized as Kaplan-Meier % (n of events).
Abbreviations as in Tables 1, 2, and 3.

The present large-scale pooled analysis afforded the opportunity to examine the outcomes with EES and PES in patients with ACS. Pooling the 4 randomized trials afforded additional power to examine subgroup outcomes, which was not otherwise possible within any single study. The results of the current study demonstrate for the first time that EES are more safe and effective than PES both in patients with ACS as well as stable CAD, with reductions in the 2-year rates of MI and ID-TLR. Moreover, treatment with EES versus PES resulted in a marked reduction in stent thrombosis in both patients with and without ACS. Indeed, the greatest absolute reductions in stent thrombosis with EES versus PES were observed in patients with non-STEMI and STEMI.

In the current analysis, treatment with EES was superior to PES throughout 2 years of follow-up in both the ACS and stable CAD cohorts, with the hazard curves continuing to diverge over time. At 30 days, the differences in the rates of MI and ID-TLR may be attributed to the higher rate of early stent thrombosis and periprocedural myonecrosis with PES, the latter most likely a result of side-branch compromise (24). At 2 years, superiority of EES can be attributed to reductions in MI, stent thrombosis, and restenosis. Importantly, there were no significant interactions between stent type and clinical syndrome on 2-year outcomes, signifying that the relative benefits of EES are consistent in both high-risk patients with ACS and lower-risk patients with stable CAD (although the absolute benefits may be greater in the higher risk ACS cohort).

As clinical syndrome acuity increased from stable CAD to unstable angina to non-STEMI to STEMI, the risk of stent thrombosis significantly increased with PES but not EES. EES thus appears to mitigate the local prothrombotic effect of ACS as a risk factor for early and late stent thrombosis. The number of patients needed to treat with EES versus PES to prevent 1 event of definite or probable stent thrombosis was 45 in the ACS cohort and 91 in the stable angina cohort. Further studies are required to completely understand the apparent disconnect between the

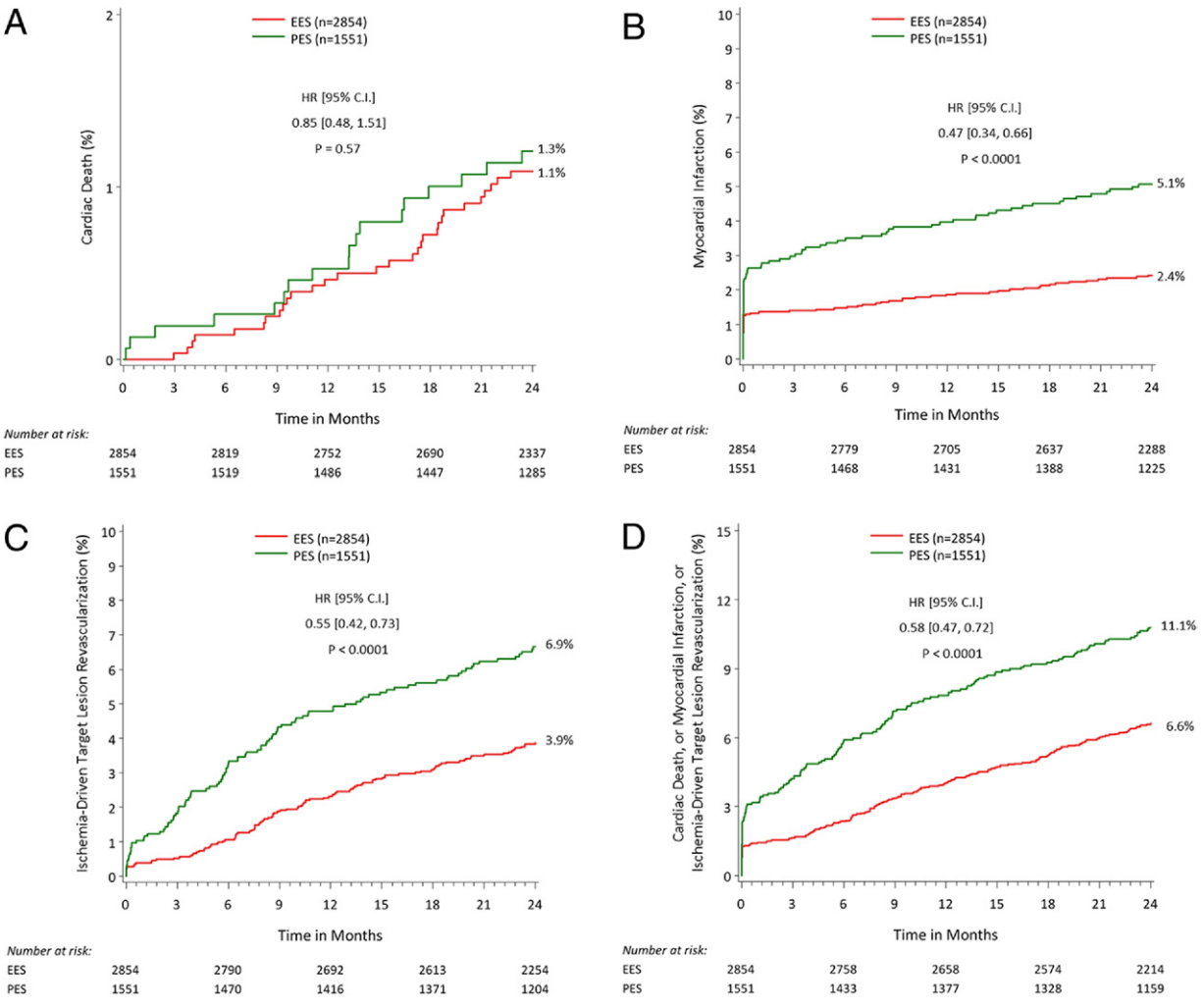

Figure 2. Time-to-Event Event Curves for Patients Presenting With Stable CAD Randomized to EES Versus PES

Two-year cumulative event curves for cardiac death **(A),** MI **(B),** ID-TLR **(C),** and the composite of cardiac death, MI, or ID-TLR **(D).** CAD = coronary artery disease; other abbreviations as in Figure 1.

potent inhibition of neointimal hyperplasia with EES and its protection from stent thrombosis. Theoretically, different mechanisms of action of the drugs or the polymers in terms of inhibition of neointimal proliferation and vascular healing may in part explain the disparity in the risk for stent thrombosis in different clinical syndromes with the 2 stents (10). Animal models have shown that the EES has more rapid and complete re-endothelialization than PES do (10). Moreover, the biocompatible fluorocopolymer used by the EES has been shown to be resistant to platelet and thrombus deposition in numerous blood-contact applications (25,26).

In the present series of trials, EES was compared with PES. Whether EES would demonstrate the same safety and efficacy profile if compared with sirolimus-eluting stents, which have greater antirestenotic efficacy than PES do (27), has not yet been tested in adequately powered randomized trials. In the recently published BASKET–PROVE (Basal Stent Kosten-Effektivitats Trial–Prospective Validation Examination) (28), no significant differences with regard to death, MI, TLR, and stent thrombosis rates were found between EES and sirolimus-eluting stents in patients with large coronary arteries (those requiring 3.0- to 4.0-mm stents).

Study limitations. This study is limited by its post-hoc nature, and the results should thus be considered hypothesis-generating. The SPIRIT trials enrolled patients with unstable angina, but excluded patients with acute or recent MI. In contrast, the COMPARE trial actively enrolled patients with non-STEMI and STEMI. Randomization was not stratified by clinical syndrome acuity in any of the enrolled studies, resulting in some differences in

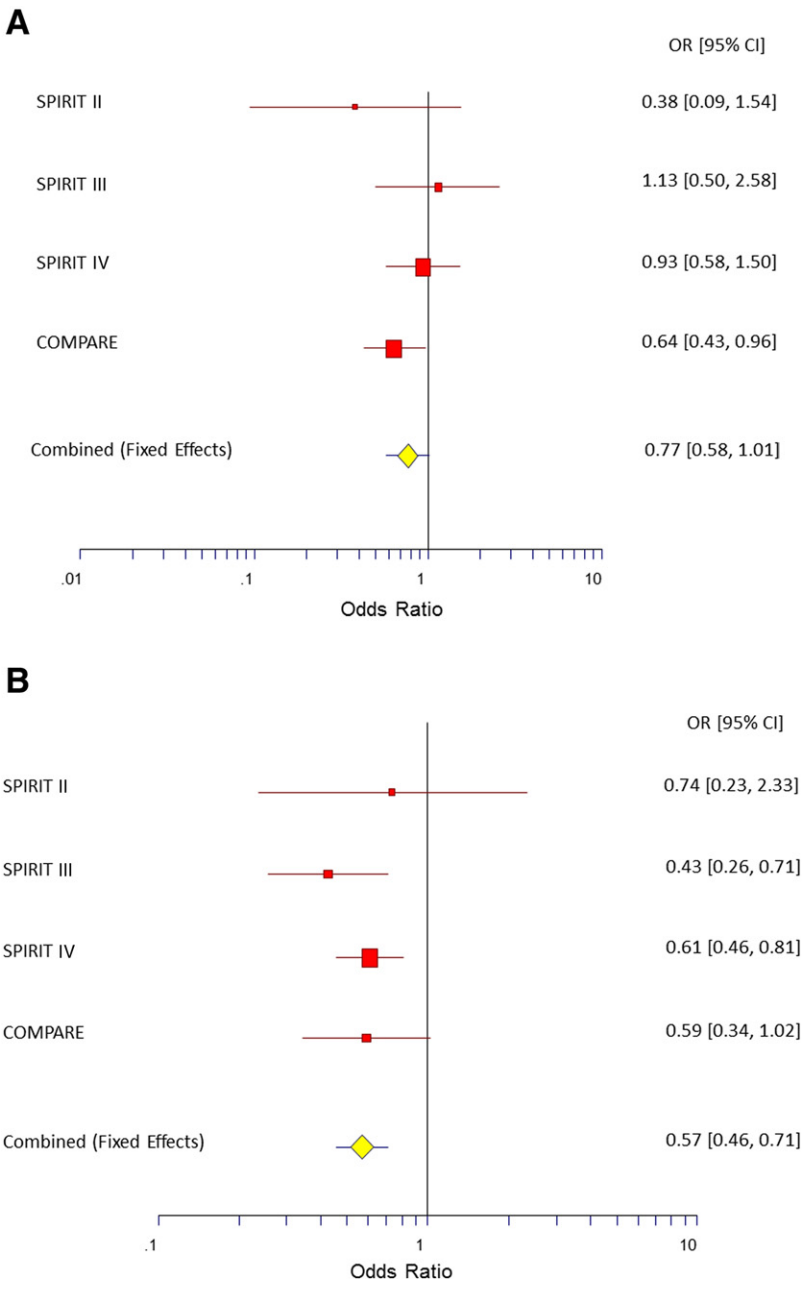

Figure 3. Odds Ratio Forest Plot (Fixed-Effects Model)

Pooled odds ratio for the composite of cardiac death, MI, or ID-TLR in patients treated with EES compared with PES in the ACS cohort **(A)** and the stable CAD cohort **(B).** The p values for heterogeneity across studies was 0.35 and 0.65 for the ACS and stable CAD cohorts, respectively. COMPARE = A Trial of Everolimus-Eluting Stents and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice; SPIRIT II = A Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients With de Novo Native Coronary Artery Lesions; SPIRIT III = A Clinical Evaluation of the Investigational Device XIENCE V Everolimus Eluting Coronary Stent System (EECSS) in the Treatment of Subjects With de Novo Native Coronary Artery Lesions; SPIRIT IV = A Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Subjects With de Novo Native Coronary Artery Lesions; other abbreviations as in Figures 1 and 2.

Table 5. Two-Year Adjusted HR for EES Compared With PES According to Clinical Syndrome Acuity

Variable	n	Events	Adjusted HR (95% CI)	p Value
ACS patients				
Death, all cause	1,996	54	0.80 (0.47–1.36)	0.41
Cardiac	2,371	37	0.79 (0.41–1.52)	0.49
Death or MI	2,336	180	0.69 (0.51–0.93)	0.01
Cardiac death or MI	1,996	103	0.68 (0.46–1.00)	0.05
Death, MI, or ID-TLR	2,359	258	0.76 (0.60–0.97)	0.03
Cardiac death, MI, or ID-TLR	2,084	182	0.76 (0.57–1.01)	0.06
Stent thrombosis				
ARC definite	2,343	27	0.18 (0.07–0.45)	0.0003
ARC definite or probable	2,323	38	0.24 (0.11–0.49)	0.0001
Stable CAD patients				
Death, all cause	4,252	96	0.86 (0.57–1.29)	0.46
Cardiac	4,399	49	0.83 (0.46–1.47)	0.51
Death or MI	4,017	205	0.63 (0.48–0.83)	0.0009
Cardiac death or MI	3,967	159	0.60 (0.44–0.82)	0.002
Death, MI, or ID-TLR	4,082	365	0.61 (0.50–0.75)	<0.0001
Cardiac death, MI, or ID-TLR	4,006	316	0.59 (0.47–0.73)	<0.0001
Stent thrombosis				
ARC definite	4,190	32	0.42 (0.21–0.84)	0.01
ARC definite or probable	4,012	41	0.36 (0.19–0.68)	0.001

The Cox model included the following covariates: stent type, age, sex, any diabetes, insulin-dependent diabetes, current smoker, hypertension, hyperlipidemia, prior CABG, prior MI, prior PCI, vessel-treated, calcification, total occlusion, thrombus, baseline TIMI flow grade 0/1, lesion length, baseline reference vessel diameter, baseline minimal luminal diameter.

TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Tables 1, 2, and 3.

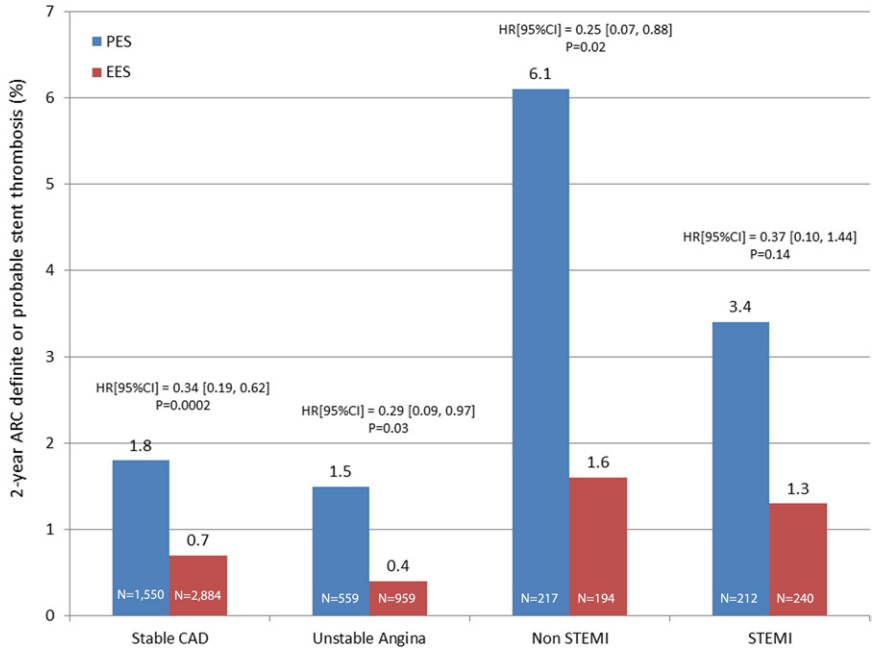

Figure 4. Stent Thrombosis Rates at 2 Years According to Clinical Syndrome Acuity in Patients Randomized to EES Versus PES

ARC = Academic Research Consortium; STEMI = ST-segment elevation myocardial infarction; other abbreviations as in Figures 1 and 2.

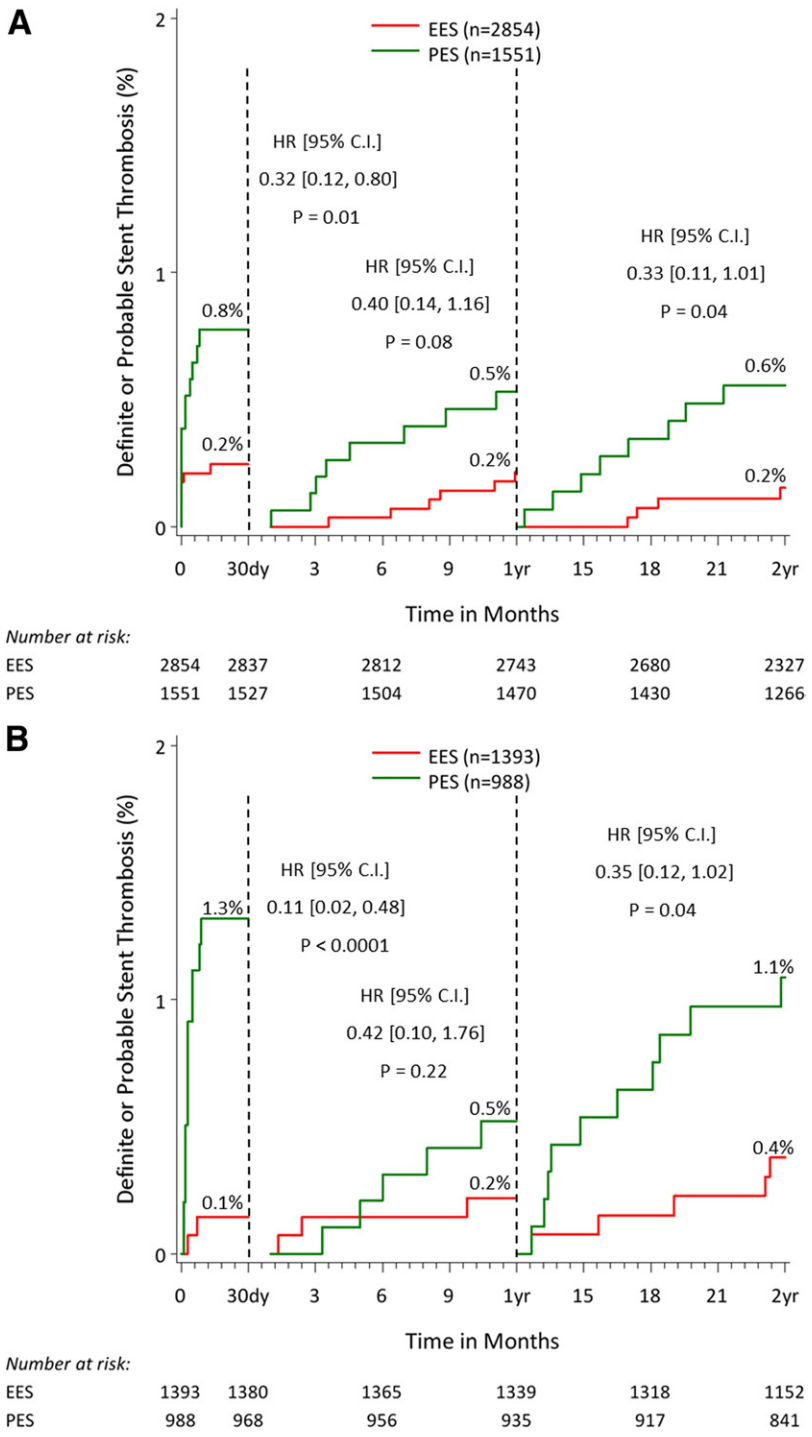

Figure 5. Landmark Analysis of Early, Late, and Very Late Stent Thrombosis According to Randomized Stent Type

Time-to-event curves with landmark analysis at 30 days and 1 year for definite or probable stent thrombosis in patients presenting with ACS **(A)** and stable CAD **(B)**. Abbreviations as in Figures 1 and 2.

baseline characteristics between the EES and PES groups in the ACS and stable CAD cohorts. Other differences between the trials were present in terms of inclusion and exclusion criteria, different randomization ratio (2:1 or 3:1 in the SPIRIT trials and 1:1 in the COMPARE trial), and the stent used in the PES arm (Taxus Express2 in the SPIRIT trials and Taxus Liberté in COMPARE). However, the multivariable adjusted hazard ratios were very similar to unadjusted hazard ratios in both the ACS and stable CAD cohorts. Finally, the operators were not blinded to stent type implanted; however, patients, caregivers, and study personnel outside the catheterization laboratory, as well as the Clinical Events Committee, were blinded to the stent type deployed.

Conclusions

In this large-scale, patient-level pooled analysis from 4 prospective, randomized trials, the use of EES compared with PES resulted in superior safety and efficacy in both patients with ACS and stable CAD, with substantial reductions observed in the 2-year rates of death or MI, stent thrombosis, and ID-TLR independent of clinical syndrome acuity.

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Key Words: acute coronary syndrome ■ drug-eluting stent(s) ■ everolimus ■ paclitaxel ■ stent thrombosis.